PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 489/02, A61K 31/435 — A1

(11) International Publication Number: **WO 96/28451**

(43) Internati nal Publication Date: 19 September 1996 (19.09.96)

(21) International Application Number: PCT/EP96/01087

(22) International Filing Date: 14 March 1996 (14.03.96)

(30) Priority Data:
195 08 664.3 — 14 March 1995 (14.03.95) — DE
PCT/EP95/01480 — 19 April 1995 (19.04.95) — WO
(34) Countries for which the regional or international application was filed: AU et al.

(71) Applicant *(for all designated States except US)*: EUROCELTIQUE S.A. [LU/LU]; 122, boulevard de la Petrusse, L-2330 Luxembourg (LU).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: MIGNAT, Christian [DE/DE]; Institut für Pharmakologie, Hospitalstrasse 4, D-24105 Kiel (DE). HEBER, Dieter [DE/DE]; Pharmazeutisches Institut, Christian-Albrechts-Universität, Gutenbergstrasse 76-78, D-24118 Kiel (DE). ZIEGLER, Albrecht [DE/DE]; Institut für Pharmakologie, Hospitalstrasse 4, D-24105 Kiel (DE).

(74) Agents: MEYERS, Hans-Wilhelm et al.; P.O. Box 10 22 41, D-50462 Köln (DE).

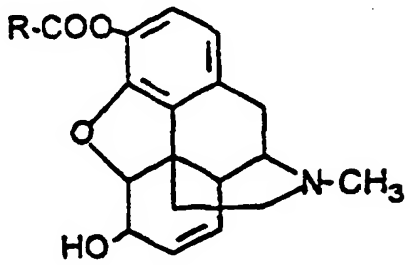
(81) Designated States: AL, AU, BB, BG, BR, CA, CN, CZ, EE, GE, HU, IS, JP, KG, KP, KR, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: MORPHINE-3-ESTERS

(57) Abstract

Disclosed are morphine-3-esters of formula (I), the enzymatic hydrolysis of which has a half-life of from 0.5 to 12 hours under physiologic conditions and the non-enzymatic hydrolysis of which has a half-life in excess of 24 hours in an aqueous medium at pH values of 6-8, especially at pH 7, except for 3-pivaloyl morphine. R is as defined in the description.



(I)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	**GB**	United Kingdom	**MW**	Malawi
AT	Austria	**GE**	Georgia	**MX**	Mexico
AU	Australia	**GN**	Guinea	**NE**	Niger
BB	Barbados	**GR**	Greece	**NL**	Netherlands
BE	Belgium	**HU**	Hungary	**NO**	Norway
BF	Burkina Faso	**IE**	Ireland	**NZ**	New Zealand
BG	Bulgaria	**IT**	Italy	**PL**	Poland
BJ	Benin	**JP**	Japan	**PT**	Portugal
BR	Brazil	**KE**	Kenya	**RO**	Romania
BY	Belarus	**KG**	Kyrgystan	**RU**	Russian Federation
CA	Canada	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CF	Central African Republic			**SE**	Sweden
CG	Congo	**KR**	Republic of Korea	**SG**	Singapore
CH	Switzerland	**KZ**	Kazakhstan	**SI**	Slovenia
CI	Côte d'Ivoire	**LI**	Liechtenstein	**SK**	Slovakia
CM	Cameroon	**LK**	Sri Lanka	**SN**	Senegal
CN	China	**LR**	Liberia	**SZ**	Swaziland
CS	Czechoslovakia	**LT**	Lithuania	**TD**	Chad
CZ	Czech Republic	**LU**	Luxembourg	**TG**	Togo
DE	Germany	**LV**	Latvia	**TJ**	Tajikistan
DK	Denmark	**MC**	Monaco	**TT**	Trinidad and Tobago
EE	Estonia	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**UG**	Uganda
FI	Finland	**ML**	Mali	**US**	United States of America
FR	France	**MN**	Mongolia	**UZ**	Uzbekistan
GA	Gabon	**MR**	Mauritania	**VN**	Viet Nam

Morphine-3-esters

The present invention relates to morphine-3-esters, drugs containing morphine-3-esters, the use of the morphine-3-esters for preparing a morphine analgesic, for the preparation of a sustained release form of morphine and a process for preparing the morphine-3-esters.

Morphine is a frequently used analgesic which in particular is used for alleviating chronic pain. For a successful pain therapy it is required that the morphine plasma level is constant. Morphine, because of its very low half-life, is administered in the form of tablets capable of a controlled release of the active ingredient or by means devices, such as pumps, for a controlled release of the active ingredient. However, these application forms are subject to hard restrictions in practice.

Slow-release morphine tablets are recognized as the most convenient option for treatment of chronic cancer pain. Adequate analgesia throughout the dosing interval with just twice- or thrice-a-day administration is achieved by incorporation of morphine into a polymer matrix from which it is gradually released during the intestinal passage. The administration of these formulations is, however, not feasible in patients who are unable to swallow tablets. The alternative use of subcutaneous or intravenous morphine infusions is limited, since sustained parenteral access and expensive pump-devices are required. These problems may be overcome by liquid slow-release morphine formulations, which would combine simplified oral or parenteral usage with prolonged

pain relief.

Another drawback of the long-term morphine administration is the occurrence of side-effects such as obstipations which may become so serious that the pain therapy using morphine will have to be discontinued or even abandoned.

It is the object of the invention to provide morphine derivatives which represent retard forms of morphine and, upon enteral application, do not exhibit any or show at least only tolerable interactions with the intestinal receptors involved.

Said object, surprisingly, is attained by morphine-3-esters, the enzymatic hydrolysis of which has a half-life of from 0.5 to 12 hours under physiologic conditions and the non-enzymatic hydrolysis of which has a half-life in excess of 24 hours in an aqueous medium at pH values of 6-8, especially at pH 7, except for 3-pivaloyl morphine.

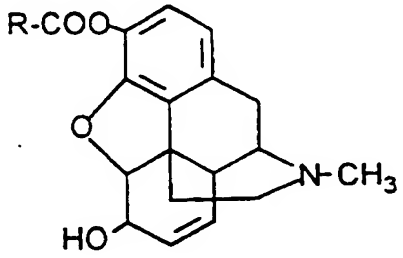
The morphine-3-esters according to the invention, due to their structure, have only weak affinity or do not have any affinity at all to the morphine receptor. The active compound is released and enabled to display its activity only after hydrolysis of the ester by specific or non-specific esterases present under physiological conditions. On the other hand, the compounds according to the invention are relatively insensitive to a non-enzymatic hydrolysis at physiological pH values, as is evident from their half-lives in excess of 24 hours in an aqueous medium at pH values of 6-8, especially at pH 7.

WO 93/03051 describes 3-morphine esters synthesized as intermediates for the preparation of morphine-6-glucuronides. WO 93/03051 fails to disclose any relevant data with respect to the activity of the 3-morphine ester derivatives described therein, especially 3-pivaloyl morphine, 3-propionyl and

3-isobutyryl morphine. Data on the rate of hydrolysis under physiological or other conditions have not been reported either.

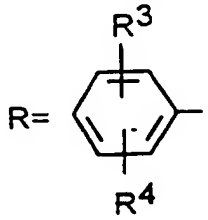
The morphine esters according to the invention are preferably characterized in that the rate of hydrolysis and/or disposition of the morphine ester for an esterolytic activity is adjusted by steric or electronic effects of the acid moiety of the morphine ester.

Morphine esters according to the invention, more specifically, are those having the following formula (I)



(I) ,

wherein R either is a moiety having the following formula (II)



(II) ,

wherein

R^3 and/or R^4 = H, if

R^3 and/or R^4 is not H, then the respective other residue independently or simultaneously has the following meaning:

R^3 and/or R^4 = straight-chain or branched alkyl group $(CH_2)_nCH_3$ with n being an integer between 0 and 10;

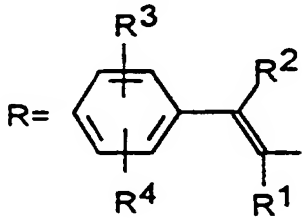
R^3 and/or R^4 is a carboxyl group or a substituted straight-chain or branched alkyl group $X-(CH_2)_nCH_3$ with n being an integer between 0 and 10, wherein X = O, S, N, -COO-;

$(CH_2)_n$-X-R^5, wherein X is as defined above and R^5 is H or an alkyl, isoalkyl, alkenyl, alkynyl, cycloalk(-en- or -yn-)yl, aryl, aralkyl, heteroaryl, heteroalkyl or cycloheteroalk(-en- or -yn-)yl moiety;
X-$(CH_2)_n$-Y-R^5, wherein Y = X, or Y independently of X has the meaning of X as defined above, R^5 is as defined above;
R^3 and/or R^4 = halogen, alkenyl, alkynyl, cycloalk(-en- or -yn-)yl, cycloheteroalk(-en- or -yn-)yl as well as aryl- and heteroaryl moities with or without -I- or -M-substituents. The phenyl moiety (II) can be substituted with R^3 and/or R^4 up to the maximum value as possible. For example, also compounds having in each o-position to a carbonyl function an alkyl moiety and in p-position a hydroxyl moiety fall within the scope of the invention.

These compounds have the appropriate hydrolysis rates.

Particularly preferred are morphine esters, wherein the substituents R^3 and R^4 are in the o- or p-positions relative to each other.

In another preferred embodiment of the invention the morphine esters are characterized in that the moiety R in formula (I) is represented by the following formula (III)



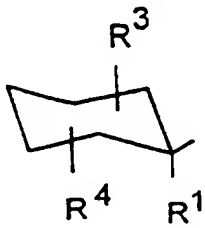
(III) ,

wherein R^1 has the meaning as defined for R^3 and R^4, with the proviso that R^1 is either equal to R^3 and/or R^4 or different therefrom; R^3 and R^4 have the meaning defined above;
R^2 stands for +M-, +I- or -I- substituents.

Especially preferred are morphine esters wherein R^2 is a substituted or free amino group to form β-aminocinnamic acid

esters.

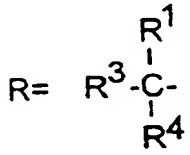
Further contemplated are morphine esters according to the invention having the formula (I) wherein R is a cycloalk(-en- or -yn-)yl of the following formula (IV)



(IV) ,

wherein R^1, R^3 and/or R^4 are as defined above, with the proviso that individual carbon atoms of the moiety R have been replaced by heteroatoms such as O, N and/or S.

Morphine esters, in a further embodiment, are characterized in that R is represented by the formula (V)



(V) ,

wherein the substituents R^1, R^3 and/or R^4 have the meanings as defined above.

As preferred morphine-3-esters there are to be mentioned 3-(2-methylbenzoyl)morphine, 3-(2-chlorobenzoyl)morphine, 3-(2,6-dichlorobenzoyl)morphine, 3-(α-methylcinnamoyl)morphine, 3-(2,6-dimethylbenzoyl)morphine, 3-(2,6-dipropylbenzoyl)morphine, 3-(2,6-diphenylbenzoyl)morphine, 3-(2-phenylbenzoyl)morphine, 3-(2,6-dimethoxybenzoyl)-morphine, 3-(2,6-diethoxybenzoyl)morphine, 3-(2-cyclohexylbenzoyl)morphine, 3-(α-methyl-ß-dimethylamino-cinnamoyl)-morphine, 3-(α-ethyl-ß-dimethylaminocinnamoyl)morphine, 3-(ß-dimethylamino-α-propyl-cinnamoyl)morphine, 3-(ß-diethylamino-α-methylcinnamoyl)morphine, 3-(ß-dibenzylamino-α-methylcinnamoyl)morphine, 3-(α-methyl-ß-phenylaminocinnamo-

yl)morphine, 3-(α-ethyl-4-methoxy-cinnamoyl)morphine, 3-(4-ethoxy-α-methyl-ß-dimethylaminocinnamoyl)morphine, 3-(1-ethylcyclohexyl-1-carbonyl)morphine, 3-(1-propylcyclohexyl-1-carbonyl)morphine, 3-(1-phenylcyclohexyl-1-carbonyl)-morphine, 3-(1-naphthylcyclohexyl-1-carbonyl)morphine, 3-(N-methyl-4-propylpiperidin-4-yl-carbonyl)morphine, 3-(N-methyl-4-phenylpiperidin-4-yl-carbonyl)morphine, 3-(2-methyl-2-phenylpropionyl)morphine, 3-(2,2-diphenylpropionyl)-morphine, 3-(2-ethyl-2-phenylbutyryl)morphine.

The morphine esters according to the invention can be used as medicaments. The medicament according to the invention contains an effective amount of at least one of the morphine-3-esters according to the invention, including 3-pivaloyl morphine. More particularly, the morphine-3-esters according to the invention may be present in the form of their pharmaceutically compatible salts, optionally in combination with further auxiliary materials and carriers.

The morphine-3-esters according to the invention, more particularly, can be used for the preparation of a morphine analgesic which avoids the side-effects caused by the morphine analgesics of prior art. As a serious side-effect, there is mentioned, by way of example, obstipation. Furthermore, the morphine-3-esters according to the invention can be utilized as a sustained release form of morphine. This sustained release form of morphine may be enterally and/or parenterally administered.

The amount to be administered in a dosage unit of morphine-3-ester corresponds to from about 0.5 mg to about 10 mg per 1 kg of body weight.

The morphine derivatives according to the invention can be prepared by a method according to J. Org. Chem. 19, 1409 (1954). In accordance therewith, a solution of morphine hydrochloride in water in the presence of sodium hydrogen-

carbonate is admixed with the appropriate carboxylic acid component, preferably an excess amount thereof, of the ester to be formed in the form of an activated derivative thereof such as an acid halide, acid anhydride *etc.*. The mixture is stirred until the reaction is complete. The reaction may be monitored, for example, by means of thin layer chromatography. The morphine-3-ester formed may be extracted, especially with water-immiscible organic solvents, such as, for example, methylene chloride. The organic solvent used for the extraction of the morphine-3-ester is evaporated, and the residue is purified, for example by column chromatography using suitable carriers such as silica gel. This method is not suitable for the preparation of 3-(2,6-dimethoxybenzoyl)morphine. The latter compound may rather be prepared by a conventional method using pyridine as a base and removal of the mono-ester by column chromatography.

The invention is further illustrated by way of the following Examples.

Chemical Procedures - Melting points were determined in open capillary tubes with a Büchi 510 melting point apparatus (Switerland) and are uncorrected. Microanalyses were carried out in the Microanalytical Laboratory of the Institute of Inorganic Chemistry, University of Kiel. All the data were close to calculated values. The structure of all the compounds were consistent with spectroscopic data (IR and ^{1}H NMR). IR spectra were recorded on a Perkin-Elmer FTIR 16 PC in potassium bromide pellets, ν in cm^{-1}. The ^{1}H NMR were determined on a Bruker ARX 300 and chemical shifts were expressed in δ (ppm) downfield from tetramethylsilane as an internal reference. Reaction progress was monitored by TLC using Kieselgel 60 F_{254} on aluminium sheets (Merck), using dichloromethane-methanol-ammonia (18:2:0,1 volume parts) as the mobile phase and detection by UV (254 and 366 nm). Purity of the compounds was verified by thin-layer chromatography and yields of products separated by column chromatography

through Kieselgel G (solvent see TLC) are given in table 1. The morphine-3-esters 2 and 10 were prepared according to literature methods.

Preparation of morphine-3-esters:

A vigorously stirred solution of 2 mmol of morphine hydrochloride in 50 ml of water is admixed in the presence of 5 g of sodium hydrogencarbonate with 10 mmol of the acid chloride in 3 equal portions. The mixture is stirred until the reaction is complete. The reaction is checked by thin layer chromatography on silica gel in an eluent system of methylene chloride/methanol/ammonia until no further reaction is detectable. Then the reaction batch is extracted with methylene chloride, the extract is dried over anhydrous Na_2SO_4 and the extractant is evaporated. The obtained residue is purified by column chromatography on silica gel using an appropriate eluent.

The physical and analytical data of the morphine-3-esters 3 - 9 and 11 are given in table 1.

Table 1 - Physical and analytical data of the morphine-3-esters 3 - 9 and 11.

Table 1

No.	Reaction Time, h	Compound	Yield	Melting point[a]	Molecular Formula
3	3	3-(2-Chlorobenzoyl)morphine	35 %	158 °C	$C_{24}H_{22}ClNO_4$
4	5	3-(2,6-Dichlorobenzoyl)-morphine	52 %	186 °C (hydrochloride 277-278 °C with decomposition	$C_{24}H_{21}Cl_2NO_4$
5	5	3-(2-Methylbenzoyl)morphine	40 %	140°C (hydrochloride 127°C)	$C_{25}H_{25}NO_4$
6	6	3-(2,6-dimethyl-benzoyl)-morphine	28 %	194 - 196°C	$C_{26}H_{27}NO_4$
7	6	3-(2,6-Dimethoxy-benzoyl)-morphine	32 %	192 - 193°C	$C_{26}H_{27}NO_6$
8	4	3-(2-Phenylbenzoyl)morphine	33 %	208 °C (hydrochloride 180 °C)	$C_{30}H_{27}NO_4$
9	5	3-(α-Methylcinnamoyl)-morphine	38 %	112 °C (as hydrochloride)	$C_{27}H_{27}NO_4$
10	-	3-Pivaloylmorphine	33 %	102 °C	-
11	6	3-(2,2-Diphenylpro-pionyl)morphine	26 %	148 °C (hydrochloride 250 °C)	$C_{32}H_{33}NO_4$

[a] Melting points are uncorrected.

Evaluation of opioid receptor binding of morphine-3-esters - Receptor binding studies were carried out using guinea-pig brain homogenates and the μ-selective [^{3}H]-[D-Ala^2, MePhe^4, Gly-ol^5] enkephalin (DAMGO), the δ-selective [^{3}H]-[D-Pen^{2,5}] enkephalin (DPDPE) and the κ-selective benzeneacetamide [^{3}H)U69593. [^{3}H]DAMGO, [^{3}H]DPDPE, and [^{3}H]U69593 (specific activity 55, 46 and 47 Ci/mmol, respectively) were purchased from Du Pont NEN Research Products (Boston, MA, USA). Unlabelled DAMGO, DPDPE, and U69593 as well as naloxone hydrochloride were obtained from Sigma Chemicals (St. Louis, MO, USA).

Brain homogenates were obtained from guniea pigs (250 - 350g b.w.), which were killed by cervical dislocation. The brain was rapidly dissected, the cerebellum removed and the remainder homogenized in 9 volumes of iced 0.32 M sucrose solution in a Potter-Elvehjem homogenizer by 5 strokes of a teflon pestle, motor driven at 1,250 rpm. The homogenate was centrifuged at 3,400 x g for 10 min and the supernatant was recentrifuged for 30 min at 115,500 x g. The pellet from the second centrifugation was suspended in 50 mM Tris-HCl buffer (pH 7.4, 4°C) by use of the Potter-Elvehjem homogenizer. The protein content of this membrane suspension was approximately 8 mg/ml, as determined by the method of Lowry et al., with bovine serum albumin as the standard. The temperature was maintained at 4°C throughout the homogenisation procedure and the membrane suspension was stored at -80°C until assay. Brain homogenates (0.25 ml) were incubated for 60 min at 25°C in a final volume of 1.5 ml of 50 mM Tris-HCl buffer (pH 7.4) containing the radioligand. In homologous competition experiments the half saturation of each ligand was determined and a radioligand concentration in the range of the half saturation concentration was used for the competition experiments. Labelled ligand was added to yield a radioactive concentration of 30 - 90 nCi/ml. Nonspecific binding was defined as the membrane-bound radioactivity remaining in the presence of 10^{-5} M naloxone.

The incubation was stopped by separating membranes from the incubation medium (filtration through glass fibre filters; Schleicher & Schuell, Dassel, Germany). The filters were pretreated with 0.15% polyethyleneimine for at least 1h. The filters were washed twice with 5 ml of ice-cold 50 mM Tris-HCl buffer (pH 7.4) and transferred to scintillation vials containing 10 ml of scintillation cocktail (Ready Protein, Beckman Instruments, Fullerton, USA). Radioactivity was determined by liquid-scintillation counting (Tri-Carb 460 CD, Packard Instruments, Downers Grove, USA). Assays were performed in quadruplicate within an experiment and each experiment was replicated 4 times.

Competition curve data were analyzed using Inplot 4.0 (GraphPad Software, San Diego, USA) computer program, yielding IC_{50} values for each drug. These values were converted to K_i values using the Cheng-Prusoff equation: $K_i=IC_{50}/(1+L/K_d)$, where IC_{50} represents the concentration of 50% inhibition, L the concentration of the respective radioligand, and K_d its affinity-constant for the receptor. K_i values of each competition curve were averaged to yield $K_i \pm$S.E.M. values.

In-vitro Hydrolysis of Morphine-3-esters - The hydrolysis of morphine-3-esters was studied in pooled human plasma. Stock solutions of the esters were freshly prepared by dissolving the compounds in 30 µl methanol subsequently diluted to 2 ml with 50 mM Tris-buffer (pH 7.4). The enzymatic reaction was initiated by adding 200 µl of stock solution to 800 µl plasma, providing an initial ester concentration of about 2 x 10^{-4}M. The mixtures were kept in a water-bath at 37°C, and at various incubation times, aliquots of 100 µl were taken. The samples were prepared immediately for HPLC analysis by the following procedure which was done within 60 seconds: the samples were diluted to 400 µl with water, vortexed, and filtrated through Millex-HV_{13} filters (0.45 µm pore size, Millipore, Bedford, Mass., USA); the filtrate was

then transferred to a vial for automatic injection and 10 µl of the solution was directly loaded onto the HPLC column without further processing.

Analytical Methodology - All chemicals were of analytical or HPLC grade and purchased from Merck (Darmstadt, Germany). Water used in the preparations of buffer solutions and mobile phases was prepared by a Seralpur PRO 90 CN system (Seral, Ransbach-Baumbach, Germany). Analysis of morphine and morphine-3-esters was performed by a HPLC system (all parts obtained from Merck, Darmstadt), consisting of a pump (L-6200A), an autosampler (AS-2000A) and a variable wavelength detector (L-4250) set at 214 nm. Separations were done on a LiChrospher 100 RO-18 guard column (5 µm particle size; 125 x 4 mm) fitted with a LiChrospher 100 RP-18 guard column (5 µm particle size, 4 x 4 mm). A flow rate of 1.2 ml/min at ambient temperature was employed. Raw data were acquired and processed by a computer software (D-6000 HPLC manager).

Two different solvent systems were used for the determination of morphine and morphine-3-ester: Solvent A (pH 3.5) was 25% (v/v) acetonitrile in an aqueous solution of 20 mM sodium dihydrogenphosphate and 1 mM sodium dodecylsulphate. Solvent B (pH 2.2) consisted of 40% (v/v) acetonitrile in 20 mM sodium dihydrogenphosphate buffer containing 1 mM sodium dodecylsulphate. The solvents were filtered using a 0.2 µm filter (Sartorius, Göttingen, Germany) and degassed under vacuum by sonication.

For monitoring ester hydrolysis, the determination of morphine and morphine-3-esters (2 - 11) was performed by isocratic elution using solvent A and solvent B, respectively. Under these conditions the retention times were 7.9 morphine, 5.0 (2), 6.1 (3), 8.4 (4), 7.0 (5), 8.9 (6), 4.5 (7), 14.1 (8), 12.3 (9), 4.9 (10), and 26.8 min (11), respectively. Two chromatographs, each of which was equilibrated with one of the both solvent systems, were

simultaneously used, thus allowing the immediate analysis of both the ester compound and morphine after a sample was taken.

The degradation of the morphine-3-esters was quantified by measuring the peak areas in relation to those of the initial peak at time zero. Half-lives for ester hydrolysis were determined from the slopes of linear plots of the logarithm of residual ester against time. At least four separate experiments were made to calculate the mean ± S.E.M. values.

Preparation of 3-(2,6-dimethoxybenzoyl)morphine:

A stirred solution of 285 mg of morphine base (1 mmol) in 2 ml of pyridine base is admixed while cooled with 500 mg of 2,6-dimethoxybenzoyl chloride (2.5 mmol) and is heated on a water bath in the absence of moisture for 30 minutes. Then the resulting product is poured into ice-water. The mixture is extracted three times with 20 ml each of methylene chloride, and the organic phase is thoroughly washed with water, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*, and the residue is purified by column chromatography.

For investigation of the opioid receptor affinity of morphine and the synthesized morphine-3-esters, their potency to inhibit radioligand binding was measured, yielding monophasic competition curves with a similar slope (ranged from 0.7 to 1.1). The concentrations of the esters required for radioligand displacement were higher than those of morphine, indicating a loss of receptor affinity of morphine by esterification at 3-position. In the present study it was found that the morphine-3-esters, when compared to morphine, were at least 15 times less active for binding to μ-, δ-, and κ-opioid receptors, respectively (table 2).

Table 2 - K_i-Values of Morphine and their Derivatives 2 - 11.

Table 2

No.	Substance name	1/affinity (relative to morphine)		hydrolysis by incubation	
		μ	δ	κ	[%]
2	3-Benzoylmorphin	16	16	17	3.0
3	3-(2-Chlorbenzoyl)-morphin	89	180	380	0.6
4	3-(2,6-Dichlor-benzoyl)-morphine	4,600	310	9,300	0.0
5	3-(2-Methylbenzoyl)-morphine	130	56	150	0.3
6	3-(2,6-Dimethyl-benzoyl)-morphine	-	-	-	0.0
7	3-(2,6-Dimethoxy-benzoyl)-morphine	200	17	2,300	0.0
8	3-(2-Phenylbenzoyl)-morphine	1,400	260	1,200	0.0
9	3-(α-Methyl-cinnamoyl)-morphine	38	36	15	2.7
10	3-Pivaloylmorphine	29	28	41	1.1
11	3-(2,2-Diphenyl-propionyl)-morphine	430	56	33	0.0

The observed inhibition potencies of compound 2, 9 and 10, however, should be considered in light of the hydrolytic lability of these esters under the conditions of the binding assay (table 2). The formation of morphine during the incubation, therefore, may have led to incorrect K_i-values, i.e. the effect of esterification of morphine on binding affinity may have been underestimated. Clearly, other factors than the contribution of morphine have to be taken into account for the relatively avid binding of the stable 2,6-dimethoxybenzoyl ester (7) to δ-sites. However, despite the differences in affinity profile, the results suggest that all morphine-3-esters tested will provide only a weak, if any, intrinsic opioid activity. By analogy with heroin or codeine, whose opioid-like effects are considered to be mediated through morphine, the pharmacologic activity of the morphine-3-esters might be also related to release of morphine by enzymatic degradation of the prodrug.

For examining the susceptibility of the compounds 2-11 to enzymatic attack, the hydrolysis rates of these esters have been determined in the presence of human plasma. In all cases the semilogarithmic plots of residual ester concentration against time revealed straight lines, suggesting that the hydrolysis obeyed pseudo-first-order kinetics (figure). The disappearance of the esters was accompanied by a corresponding increase in morphine (data not shown). An evidence that the conversion of the esters is mainly due to esteratic activity is given by the comparatively low rate of spontaneous hydrolysis in the absence of plasma. Concerning the hydrolysis rates in plasma, a quite different pattern became evident: while the most labile compounds (2, 3, 9) are hydrolyzed with a half-life of below 1 h, others (4, 7, 8) were hardly affected, yielding half-lives which exceeded 300 h (table 3).

Table 3 - Hydrolysis of morphine-3-esters in 80% human plasma and aqueous buffer solution, respectively (pH 7.4, 37°C). Values are given as means ± S.E.M. of 4-8 experiments.

Table 3

Compound No.	Human Plasma 80%		Tris-buffer 50 mM
	$t_{1/2}$(h)	hydrolyzed in 24h (%)[a]	hydrolyzed in 24 h (%)
2	0.62 ± 0.04	100	35
3	0.93 ± 0.04	100	9
4	> 300	< 5	0
5	22.7 ± 1.9	52	1
6	62.5 ± 9.6	23	0
7	> 300	< 5	0
8	> 300	< 5	0
9	0.46 ± 0.05	100	22
10	9.4 ± 0.5	83	4
11	56.5 ± 2.8	26	0

[a] Calculated from half-lives.

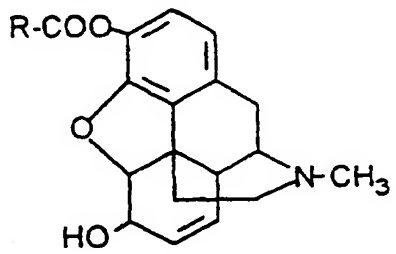
Concerning the applicability of the morphine-3-esters for prolonging the release of morphine under in vivo conditions, definitive conclusion cannot be drawn on the basis of the above results. Due to the esteratic activity localized in erythrocytes, liver, and brain tissue, rates of hydrolysis measured in vitro are usually less than those attained in vivo.

C L A I M S :

1. A morphine-3-ester, the enzymatic hydrolysis of which has a half-life of from 0.5 to 12 hours under physiologic conditions and the non-enzymatic hydrolysis of which has a half-life in excess of 24 hours in an aqueous medium at pH values of 6-8, especially at pH 7, except for 3-pivaloyl morphine.

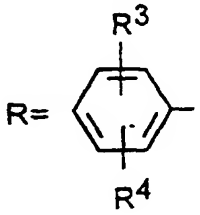
2. The morphine-3-ester according to claim 1, characterized in that the rate of hydrolysis and/or disposition of the morphine ester for an esterolytic activity is adjusted by steric or electronic effects of the acid moiety of the morphine ester.

3. The morphine-3-ester according to claims 1 and/or 2, which has the following formula (I)



(I) ,

wherein
R either is a moiety having the following formula (II)



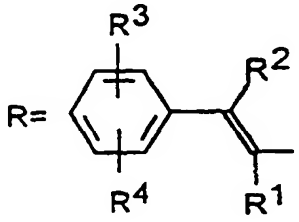
(II) ,

wherein
R^3 and/or R^4 = H, if
R^3 and/or R^4 is not H, then the respective other residue independently or simultaneously has the following meaning:
R^3 and/or R^4 = straight-chain or branched alkyl group $(CH_2)_nCH_3$

with n being an integer between 0 and 10;
R^3 and/or R^4 is a carboxyl group or substituted straight-chain or branched alkyl group $X-(CH_2)_nCH_3$ with n being an integer between 0 and 10, wherein X = O, S, N, -COO-; $(CH_2)_n-X-R^5$, wherein X is as defined above and R^5 is H or an alkyl, isoalkyl, alkenyl, alkynyl, cycloalk(-en- or -yn-)yl, aryl, aralkyl, heteroaryl, heteroalkyl or cycloheteroalk(-en- or -yn-)yl moiety;
$X-(CH_2)_n-Y-R^5$, wherein Y = X, or Y independently of X has the meaning of X as defined above, R^5 is as defined above;
R^3 and/or R^4 = halogen, alkenyl, alkynyl, cycloalk(-en- or -yn-)yl, cycloheteroalk(-en- or -yn-)yl as well as aryl- and heteroaryl moities with or without -I- or -M-substituents.

4. The morphine-3-ester according to claim 3, characterized in that the substituents R^3 and R^4 are in the o- or p-positions relative to each other and/or up to the maximum positions of the phenyl moiety or formula II are substituted by R^3 and/or R^4.

5. The morphine-3-ester according to claim 3, characterized in that the moiety R in formula (I) is represented by the following (III)



(III) ,

wherein R^1 has the meaning as defined for R^3 and R^4, with the proviso that R^1 is either equal to R^3 and/or R^4 or different therefrom; R^3 and R^4 have the meaning as defined in claim 3, R^2 stands for +M-, +I- or -I- substituents.

6. The morphine-3-ester according to claim 5, characterized in that R^2 is a substituted or free amino group such as to form a β-aminocinnamic acid ester.

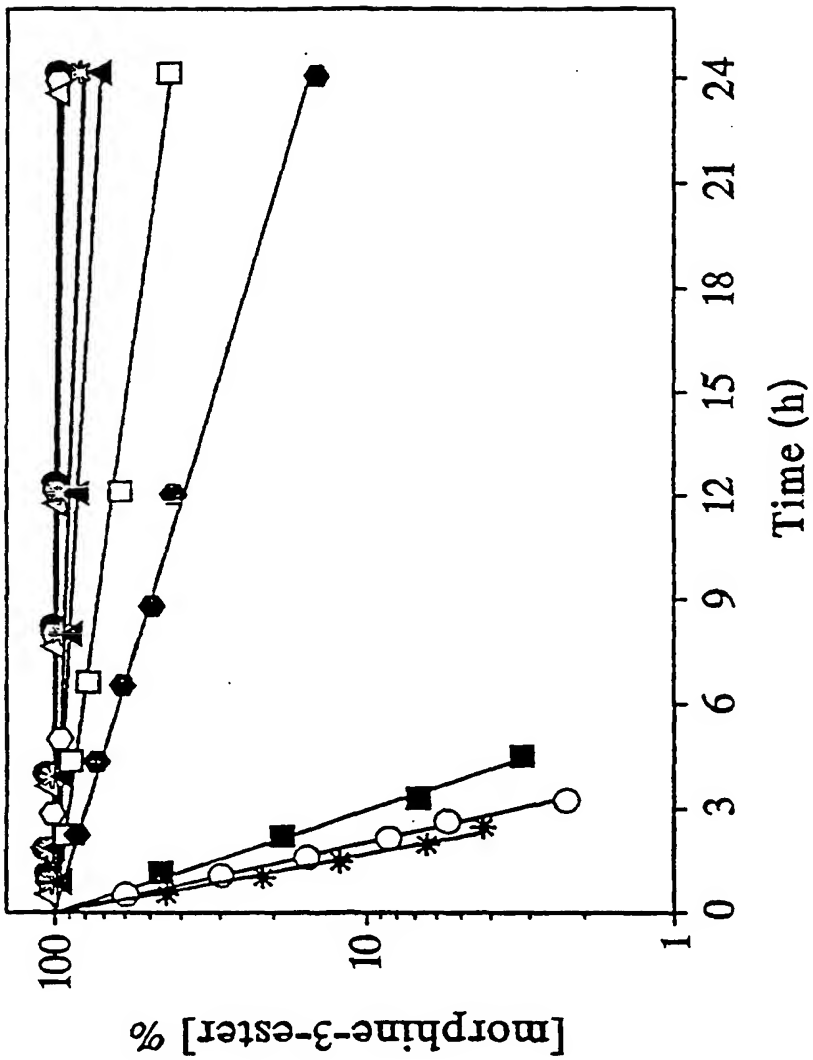


Fig. In vitro hydrolysis of morphine-3-esters in 80% human plasma at 37°C: II (○), III (■), IV (○), V (□), VI (✱), VII (●), VIII (△), IX (✱), X (●), and XI (▲). Each symbol represents the mean of 4-8 experiments.

INTERNATIONAL SEARCH REPORT

tional Application No
PCT/EP 96/01087

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D489/02 A61K31/435

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,93 03051 (SALFORD UTLRAFINE CHEMICALS) 18 February 1993 cited in the application see page 7, line 3 ---	1-13
X	WO,A,92 08459 (KABI PHARMACIA) 29 May 1992 see page 5 - page 6; claim 1 ---	1-13
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

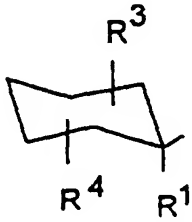
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 May 1996	25.07.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Gettins, M

Form PCT/ISA/210 (second sheet) (July 1992)

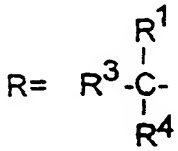
7. The morphine-3-ester according to claim 3, characterized in that R is a cycloalk(-en- or -yn-)yl of the following formula (IV)



(IV) ,

wherein R^1, R^3 and/or R^4 are as defined above, with the proviso that individual carbon atoms of the moiety R have been replaced by heteroatoms such as O, N and/or S.

8. The morphine-3-ester according to claim 3, characterized in that R is represented by the formula (V)



(V) ,

wherein the substituents R^1, R^3 and/or R^4 have the meanings as defined above.

9. 3-(2-methylbenzoyl)morphine, 3-(2-chlorobenzoyl)morphine, 3-(2,6-dichlorobenzoyl)morphine, 3-(α-methylcinnamoyl)morphine, 3-(2,6-dimethylbenzoyl)morphine, 3-(2,6-dipropylbenzoyl)morphine, 3-(2,6-diphenylbenzoyl)morphine, 3-(2-phenylbenzoyl)morphine, 3-(2,6-dimethoxybenzoyl)morphine, 3-(2,6-diethoxybenzoyl)morphine, 3-(2-cyclohexylbenzoyl)morphine, 3-(α-methyl-ß-dimethylamino-cinnamoyl)-morphine, 3-(α-ethyl-ß-dimethylaminocinnamoyl)morphine, 3-(ß-dimethylamino-α-propyl-cinnamoyl)morphine, 3-(ß-diethylamino-α-methylcinnamoyl)morphine, 3-(ß-dibenzylamino-α-methylcinnamoyl)morphine, 3-(α-methyl-ß-phenylaminocinnamoyl)morphine, 3-(α-ethyl-4-methoxy-cinnamoyl)morphine, 3-(4-ethoxy-α-methyl-ß-dimethylaminocinnamoyl)morphine, 3-(1-ethylcyclohexyl-1-carbonyl)morphine, 3-(1-propylcyclo-

hexyl-1-carbonyl)morphine, 3-(1-phenylcyclohexyl-1-carbonyl)-morphine, 3-(1-naphthylcyclohexyl-1-carbonyl)morphine, 3-(N-methyl-4-propylpiperidin-4-yl-carbonyl)morphine, 3-(N-methyl-4-phenylpiperidin-4-yl-carbonyl)morphine, 3-(2-methyl-2-phenylpropionyl)morphine, 3-(2,2-diphenylpropionyl)-morphine, 3-(2-ethyl-2-phenylbutyryl)morphine.

10. A medicament, comprising an effective amount of at least one of the compounds as set forth in claims 1 through 9, including 3-pivaloyl morphine, or a pharmaceutically compatible salt thereof, optionally in combination with further auxiliary materials and carriers.

11. Use of the substances according to claim 10 for the preparation of a morphine analgesic to avoid side-effects such as obstipation.

12. Use of the substances according to claim 10 for the preparation of a sustained release form of morphine that may be enterally and/or parenterally administered.

13. A process for preparing the compounds according to any one of claims 1 through 9 by esterification of morphine in the 3-position with the appropriate ester components.